REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 332-366 are in the case.

I. THE INTERVIEW

At the outset, the undersigned wishes to thank the Examiner (Ms. Emily Le) and her supervisor (Mr. James Housel), for kindly agreeing to conduct an interview in this application. The interview was held on October 12, 2004, and was attended by Dr. Robert Lorence, co-applicant in the present application, as well as by Thomas Byrne, Esq. and the undersigned, counsel representing Wellstat Biologics Corporation, the assignee corporation. The courtesies extended by the Examiner and her supervisor were most appreciated. The substance of the interview will be clear from the comments contained in the Interview Summary Record and from the discussion presented below.

II. SPECIFICATION

The specification has been amended to update the status of the parent application. The objection regarding the Field of Invention and Summary of the Invention was discussed with the Examiner and her supervisor during the interview. Agreement was reached that no changes, other than updating the reference to the parent application, are required to the specification. Withdrawal of the objections to the specification is accordingly respectfully requested.

III. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 350-352 stand rejected under 35 U.S.C. §112, second paragraph, on the ground that the expression "the amount" has insufficient antecedent basis. In response, claims 350-352 have been amended to deal with this point. No new matter is entered. Withdrawal of the outstanding formal rejection is now respectfully requested.

IV. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 332-355 stand rejected under 35 U.S.C. § 112, first paragraph, on alleged lack of enablement grounds. In particular, the Examiner has stated:

> "The specification, including the working examples provided, teaches that at different concentrations of NDV, tumor regression is observed in mice that have been xenografted with human tumor cells. However, the specification does not teach how such finding would correlate to the use of NDV in mammals, including humans and non-human animals having a tumor. Therefore, the specification, including the working examples, is not enabling for one skilled in the art to practice the claimed invention."

The Examiner has further stated:

> "However, the prior art also teach that there is an inconsistency and lack of reproducibility of xenografted tumor growth in mice. (See Sharkey et al. in "Experience in Surgical Pathology with Human Tumor Growth in the Nude Mouse". The Nude Mouse in Experimental Research, 1978, Chapter 10, pp 187-214.)"

In response, Dr. Lorence at the interview drew attention to the following documents (copies of which are enclosed with the present response):

- Povlsen, "Status of Chemotherapy, Radiotherapy, Endocrine Therapy, and Immunotherapy Studies of Human Cancer in the Nude Mouse", Ch. 19, 437-

456 (1978), from the book "The Nude Mouse in Experimental and Clinical Research", Ed. Fogh and Giovanella, Acad. Press, 1978);

- Steven H. Thorne and David H. Kirn, "Future directions for the field of oncology virotherapy: a perspective on the use of vaccinia virus", Expert Opin. Biol. Ther., 4(8), 1307-1321 (2004);

- Poster: "Slow Intravenous Infusion of PV701, an Oncolytic Virus: Final Results of a Phase I Study", Am. Soc. Clin. Oncology (ASCO Meeting) (2004)

Referring to the Examiner's assertion that the specification "does not teach" how the findings in the Examples would "correlate" to the use of NDV in mammals, including human and non-human mammals having a tumor, Dr. Lorence drew attention to the fact that the cited Sharkey et al. reference (Chapter 10 of the book "The Nude Mouse in Experimental and Clinical Research", Ed. Fogh and Giovanella, Acad. Press, 1978) does not address the usefulness of the human tumor xenograft model to predict sensitivity of tumors to anticancer agents. Dr. Lorence stressed that, in Sharkey et al., there is no mention of any tumor being treated. Sharkey, rather discusses the low rate of forming tumors from human tissue and the variability of growth rate which are not relevant to the issue of correlation of human tumor xenograft data in mice with efficacy in other mammals including humans

Dr. Lorence then turned to Povlsen (Chapter 19 (copy attached) of the same book containing Sharkey et al. (Chapter 10), cited by the Examiner), and pointed to the statement in Section E on page 449 which states:

> "From the already-reported data from several laboratories (Povlsen et al., 1973; Povlsen and Rygaard, 1974; Povlsen and Jacobsen, 1975; Giovanella *et al.*, 1977; Ovejera and Barker, 1977), it can be concluded that, in general, the responses to chemotherapy of different types of human tumors transplanted in nude mice resemble those observed in clinical investigations."

Based on the above, it is clear that, as of the 1993 effective filing date of the present application, one of ordinary skill in the art, based on the working examples in the present application, would have had a reasonable expectation that the results reported in the application would correlate to activity in mammals, including humans. Agreement was reached on this point during the interview. Withdrawal of this aspect of the lack of enablement rejection is accordingly respectfully requested.

On page 4 of the Action, the Examiner has taken the position that:

> "Although the state of the art teach [sic] that NDV-based anticancer therapy has been reported to be of benefit in different clinical studies. However, the overall level of evidence that is provided does not support the virus' role in cancer as an anticancer agent. The use of NDV as an anticancer agent is not conclusive, as noted by National Cancer Institutes Complementary and Alternative Medicine (CAM) on NDV. Therefore, due to the lack of evidence that would provide a nexus between NDV and the regression of tumors in mammals having a tumor, the quantity of experimentation required of one skilled in the art to practice the claimed invention would be tremendous for the following reasons ..."

The Examiner has further asserted:

> "With the exception of item (vii), all of the listed items are discussed by Kirn et al. As factors that must be considered in selecting a virus for use in anticancer therapy and the factors that influence efficacy of such therapy. (See Kirn et al. "Replicating Viruses as Selective Cancer Therapeutics". Molecular Medicine Today, 1996, 519-527.)"

In response to the Examiner's statement that the use of NDV as an anticancer agent is not "conclusive", Dr. Lorence noted during the interview that the portion of the NCI CAM Report cited by the Examiner relates to "Human/Clinical Studies" and the term "inconclusive" refers to the lack of phase III human clinical trial results, and is not a general statement by the NCI with respect to NDV. Dr. Lorence, in addition, pointed to the newly published article (August, 2004) naming Kirn as a co-author (the same person as in Kirn et al. cited by the Examiner), in which it is stated at page 1308:

> "The Newcastle disease virus PV701 (Wellstat Biologics, MD, USA) demonstrated intravenous efficacy in a Phase I trial"

Dr. Lorence also drew attention to the Poster presented at the ASCO Meeting (the NCI was not aware of the results presented in the Poster when the CAM Report was published), which presented favorable results using PV701 in a Phase I study (Dr. Lorence confirmed that "PV701" is triple plaque purified MK107, and MK107 is referred to in the disclosure and one of the claims of the present case). Attention is drawn in particular to the results presented in the boxes of figures with patient radiographic scan results on the right hand side of the Poster entitled "Efficacy" in which pronounced tumor regressions were noted in the patients after treatment with PV701.

For all of the above reasons, it is believed that the lack of enablement rejection should now be withdrawn. Such action is respectfully requested.

V. PUBLIC AVAILABILITY OF NDV STRAIN 73-T

During the interview, the Examiner requested evidence of public availability of the NDV strain 73-T (which strain is recited in claims 338, 349 and 362) (see the Interview Summary Record). In response, attached are copies of the following documents that indicate a wide distribution of strain 73-T and that several other investigators besides Cassel and the inventors (Lorence and Reichard) have performed experiments with 73-T:

- Schirrmacher et al. (German Cancer Research Center, Heidelberg, Germany) 1997 Clin Cancer Res 3:1135. This paper states: "NDV 73-T [is] from W A. Cassel (Atlanta, GA)".

- Zorn et al. (Division of Hematology and Oncology, University Medical Center, Hannover, Germany) 1994 Cancer Biotherapy 9:225-235. This paper states: "Newcastle disease virus (NDV) strain 73-T was provided by Dr. Ruhl from the Department of Poultry Diseases of the Veterinary University of Hannover". Thus, both Dr. Ruhl and Dr. Zorn were able to obtain NDV 73-T.

- Plager et al. (MD Anderson Hospital, Houston TX), two abstracts, one from 1985 and the other from 1986, both entitled: Adjuvant immunotherapy with Newcastle disease virus oncolysate of M.D. Anderson (MDAH) stage III-B Malignant Melanoma: 1985 (Proc of Am Soc Clin. Oncol. 4:150) and 1986 (Proc of Am Soc Clin. Oncol. 5:137). Both of these abstracts indicate the use of cell lines and virus as Cassel et al., and thus indicates the use of NDV 73-T (since Cassel used 73-T for his oncolysate work).

- Sateesh Krishanmurthy, Toru Takimoto and Allen Portner (from St. Jude's Children's Hospital in Memphis, TN, USA) in 2002 published an abstract entitled: "Newcastle disease virus as an oncolytic agent: Mechanism of viral infection, growth and oncolysis" at the 21st Annual Meeting of the American Society for Virology (page 90 of abstract book, abstract #W15-8). In the abstract, strain 73-T is mentioned. Verification that strain 73-T was included in experiments by the authors is provided by the email from Dr. Allen Portner to Dr. Lorence dated October 13, 2004 (attached).

- Batliwalla FM et al. 1998 paper (authors at various institutions in the USA including New York University in Manhasset and Emory University and Veterans Affairs Medical Center in Atlanta). Page 793 (lines 5-9) of the discussion in Batliwalla et al. indicates that: "To address this issue, studies are in progress in which chronic immunization of mice with T73 oncolytic strain of NDV will be compared with the nonlytic Ulster strain in a melanoma model system." A 2001 publication by Bonaccorsi, Ansel and Armstrong (Dematology Clinics, 19:727-735) which includes two of the same authors (Ansel and Armstrong) as in Batliwalla et al. paper further substantiates this on page 731, 2nd column, lines 2-7: "We have recently reinitiated preclinical studies with NDV oncolysate in a murine melanoma model with the long-term aim of generating more information on the mechanism of action of NDV in order to reinitiate clinical trials."

It is believed that the above establishes public availability of NDV strain 73-T.

VI. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

It was agreed during the interview that the obviousness-type double patenting rejections will be placed in abeyance pending a determination of allowability of the present claims. Once that has been determined, the Office proceed in accordance with Office procedure. At present, none of the pending cases referred to in the obviousness-type double patenting rejection is close to allowance. It would therefore appear that the present application, once in allowable condition, should proceed with issuance of the official notice of allowance.

VII. AMENDED AND NEW CLAIMS

As agreed during the interview, the independent claims have been amended to specify that the NDV administered is "live". Basis appears at page 23, line 17. In addition, new dependent claims 356-366 are presented to round out the protection in this case. Claims 356-364 use the same language as existing dependent claims 344-349, 351 and 352, and are dependent on claim 355. Support for claims 356-364 can be found, *inter alia*, on pages 11, line 12 to page 13, line 35. New dependent claims 365 and 366 have been added. Support for "cervical carcinoma" can be found, *inter alia*, on page 11, line 16. "Cervical carcinoma" is already recited in claims 333 and 344. No new matter is entered. Entry of the amendments is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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